PATENT
Atty. Docket No.: 56819-403001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 6721
Werner Oberegger, et al.	Examiner: Susan T. Tran
Application No.: 10/507,525	Technology Center/Art Unit: 1615
Filed: September 14, 2004	
For: MODIFIED-RELEASE TABLET OF BUPROPION HYDROCHLORIDE	APPELLANTS' BRIEF UNDER 37 C.F.R. §41.37
Customer No.: 21967	

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This brief is filed pursuant to 37 C.F.R. §41.37, following the Notice of Appeal filed concurrent herewith. Also submitted with this brief is authorization to pay the fee as set forth in 37 C.F.R. §41.20(b)(2).

TABLE OF CONTENTS

I.	**REAL PARTY IN INTEREST**	Page 3
II.	**RELATED APPEALS AND INTERFERENCES**	Page 3
III.	**STATUS OF THE CLAIMS**	Page 3
IV.	**STATUS OF THE AMENDMENTS**	Page 3
V.	**SUMMARY OF CLAIMED SUBJECT MATTER**	Page 3
VI.	**GROUNDS OF REJECTION TO BE REVIEWED AND APPEALED**	Page 6
VII.	**ARGUMENT**	Page 7
VIII.	**CLAIMS APPENDIX**	Page 52
IX.	**EVIDENCE APPENDIX**	Page 55

I. REAL PARTY IN INTEREST

The real party in interest in U.S. Application No. 10/507,525 is Biovail Laboratories Inc.

II. RELATED APPEALS AND INTERFERENCES

None.

III. STATUS OF THE CLAIMS

Claims 155-172 are pending in this application. In the final Office Action mailed July 14, 2006, the Examiner rejected claims 155-172 under 35 U.S.C. §112, first paragraph, alleging that these claims fail to comply with the written description requirement. Additionally, these same claims were apparently rejected under 35 USC §112 first paragraph as allegedly failing to enable the claimed invention. The Examiner also rejected claims 155-172 under 35 U.S.C. §112, second paragraph, alleging that they are indefinite. Further, the Examiner further rejected claims 155, 156, 159-162, 165-167, and 169-171 under 35 USC §102(e) as allegedly being anticipated by Li et al., US2003/0161874. All of these §112 and §102 rejections of claims 155-172 are appealed herein.

IV. STATUS OF THE AMENDMENTS

No amendment was filed subsequent to the final Office Action of July 14, 2006.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter in this appeal relates to a modified-release tablet suitable for use in a once-daily administration of bupropion treatment regimen in patients in need of such bupropion administration wherein such modified-release tablet is "bioequivalent" to Wellbutrin® or Zyban/Wellbutrin® SR (sustained release) tablets over a 24 hour period when said modified-release tablet is administered in a once-a-day bupropion treatment regimen to a patient in need of such bupropion administration.

For the reasons set forth infra, the meaning of "bioequivalent" in the context of the claimed invention would be apparent to one of ordinary skill in the relevant modified-release drug formulation art and further based on the express teachings of this application. Particularly, "bioequivalent" means that certain pharmacokinetic parameters, i.e., Cmax values (maximum concentration of drug in the plasma) and AUC values (area under the curve which represents drug levels in the plasma over a set time), and which PK parameters are conventionally used to assess the in vivo release properties of modified-release tablet compositions such as claimed herein do not exhibit a significant difference in the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. (See e.g., Paragraph [0016] of this application).

More specifically, the subject application makes clear that the subject claimed modified-release tablets are "bioequivalent" to Wellbutrin® or Zyban/Wellbutrin® SR tablets wherein "bioequivalent" is defined according to accepted FDA guidelines which require that these modified-release tablets possess specific pharmacokinetic parameters (AUC 0-inf, AUC 0-t, and Cmax values) such that the 90% confidence interval (CI) of the ratio of the geometric means for AUC 0-inf or AUC 0-t and Cmax to the same PK parameters for Wellbutrin® or Zyban/Wellbutrin® SR are within 80-125% when the subject modified-release tablet is administered in a once-a-day treatment regimen. (See e.g. paragraphs [0140], [0148], [0155], [0156] and [0174] of the subject specification).

As discussed in the subject application, the claimed invention provides an improvement over previous bupropion formulations art because the subject modified-release tablet is only administered once daily thereby enhancing patient compliance which is a prevalent concern in the relevant bupropion treated population (depressed individuals). Essentially, once-daily administration increases the likelihood that these individuals will adhere to the prescribed therapy and be effectively treated.

The claimed modified-release tablets additionally may comprise a moisture barrier coating that enhances stability and which precludes degradation of the bupropion

contained therein when the tablets are stored at 25+/- 2 degrees C at 60% +/- 5 % relative humidity (see claim 158).

The claimed bioequivalent tablets also in particular comprise a polymeric control-releasing coat surrounding a bupropion containing core that controls the release of bupropion from the modified-release tablet which is in turn surrounded by said moisture barrier layer. (See Claims 168 and 172)

Still further, the subject bioequivalent modified-release tablets preferably do not exhibit any food effect, i.e., they exhibit the same bioequivalency in vivo when the modified-release tablets are administered as part of a once daily treatment regimen to patients in a fed or fasted state. (Claims 156 and Claim 159). This similarly enhances patient compliance since once-daily administration of the subject bupropion medicament can be effected before or after eating without compromise to drug efficacy.

Subject Matter Recited in The Only Independent Claim 155

The claimed subject matter as set forth in the only independent claim 155 is directed to a modified-release tablet suitable for use in a once-daily administration of bupropion treatment regimen in patients, in need of such bupropion administration, wherein such modified-release tablet is bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR tablets when said modified-release tablet is administered in a once-a-day bupropion treatment regimen to a patient in need of such bupropion administration. Wellbutrin® and Zyban/Wellbutrin® SR are both FDA approved bupropion medicaments for the treatment of depression and smoking cessation. Unlike the subject once-day bupropion containing modified-release tablet, Wellbutrin® and Zyban/Wellbutrin® SR tablets must be administered three or four times daily (Wellbutrin®) or twice daily (Zyban/Wellbutrin® SR). (See specification at paragraph [004]).

Literal and implicit support for a bioequivalent modified-modified bupropion containing tablet as set forth in Claim 155 can be found in the specification, *e.g.*, in paragraph [0016] and from paragraphs [0140], [0148], [0155-0156] and [0174] which make clear that "bioequivalent" modified-release tablet compositions according to the invention are assessed according to accepted FDA guidelines and more particularly refers to the fact that the 90%

confidence interval for the ratios of the geometric means for AUC 0-inf; AUC 0-t; and Cmax parameters possessed by modified-release tablets according to the claimed invention to that of Wellbutrin® or Zyban/Wellbutrin® SR (when the subject modified-release tablet is administered once-daily as part of a once-a-day bupropion treatment regimen to a subject in need thereof in the presence or absence of food) are within 80-125%. Bioequivalent modified release tablets possessing the above-described properties were novel and non-obvious at the time of the present invention and possess advantageous properties relative to all previously available and FDA approved bupropion medicaments. Modified-release tablets according to the invention are now sold by GlaxoSmithKline under the Tradename Wellbutrin® XL.

VI. GROUNDS OF REJECTION TO BE REVIEWED AND APPEALED

1. The rejection of claims 155-172 for alleged lack of written description is improper because the present application would reasonably convey to the ordinarily skilled artisan the inventors' possession of the claimed invention, particularly in view of the state of the art, and further because the express teachings of the specification including the working examples would place an ordinarily skilled artisan in possession of the claimed invention upon reading the present application.

2. The rejection of claims 155-172 for alleged failure to comply with the enablement requirement of 35 USC §112 first paragraph is improper because the teachings of the specification would enable a skilled artisan to produce the claimed bioequivalent modified-release bupropion tablets that are suitable for once-daily administration absent undue experimentation.

3. The rejection of claims 155-172 for alleged lack of definiteness and indeterminate scope is improper because the ordinarily skilled artisan would readily comprehend how to assess whether a modified-release tablet is bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR as claimed herein since Wellbutrin® and Zyban/Wellbutrin® SR are both commercially available FDA approved drugs for treating depression and possess pharmacokinetic (PK) parameters according to FDA therapeutic guidelines for these specific

drugs which cannot be altered and which correspond to those PK parameters (AUC 0-inf; AUC 0-t; and Cmax) which are used to define bioequivalency herein and further because the recitation of the Tradenames herein precisely defines the scope of the claimed invention.

4. The rejection of claims 155-156, 159-162, 165-167 and 169-171 under 35 USC §102(e) as allegedly being anticipated by the teachings of Li et al., US2003/0161874 is improper since the Patent Office has not met its burden of reasonably establishing that Li et al., US2003/0161874 teaches a modified-release tablet that is bioequivalent to Wellbutrin® or Zyban/Wellbutrin® wherein "bioequivalent" is defined according to accepted FDA guidelines and means that the modified-release tablet claimed in Claims 155-156, 159-162, 165-167 and 169-71 possesses PK parameters (AUC 0-inf, AUC 0-t, and Cmax) such that the 90% confidence interval (CI) corresponding to the ratios of the geometric means thereof to the same PK parameters for Wellbutrin® and Zyban/Wellbutrin® SR are within 80-125% when the claimed modified-release tablet is administered to a patient in need of bupropion administration as part of a once-a-day treatment regimen.

VII. ARGUMENT

A. The Rejection of Claims 155-172 Based on Indefiniteness Because of Their Referral to Tradenames is Unsustainable

The Examiner has rejected claims 155-172 under 35 U.S.C. §112, second paragraph, alleging that the claims are indefinite and of indeterminate scope because of the referral in Claim 155 to Wellbutrin® and Zyban/Wellbutrin® SR. The Examiner alleges that the claims are improper because a trademark or tradename is improperly used as a limitation to identify or describe the claimed modified release tablets. Appellants respectfully traverse the rejection and respectfully submit that the recitation of the tradenames Wellbutrin® and Zyban/Wellbutrin® SR should be permitted herein since this language does not render the claims indefinite or of indeterminate scope but rather precisely defines the scope of the invention.

1. Standard for Definiteness

According to the MPEP, the Examiner's focus in deciding whether the claims satisfy the definiteness enablement requirement of 35 U.S.C §112, second paragraph should be whether the claim meets the threshold requirements of clarity and precision not whether more suitable language or modes of expression are available. MPEP §2173.0264. The essential inquiry to this requirement is whether the claim sets out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language mist be analyzed not in a vacuum, but in light of:

(A) The content of the particular application disclosure;

(B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

The MPEP further states in MPEP 2173.05(u) that the presence of a trademark or tradename in a claim is not *per se* improper, but that the claim should be carefully analyzed to determine how the mark or name is used in the claim. The MPEP indicates that the use thereof as a claim limitation to describe a particular product is improper. By contrast, the MPEP indicates that if it (tradename or trademark) is not intended as a limitation that its use may still be improper if its presence in the claim causes confusion as to the scope of the claim. MPEP §2173.05

2. The Recited Tradenames Do Not Cause Confusion Because the Claim Scope and the Meaning Thereof Would Be Clear to One Possessing Ordinary Skill in the Art at the Time This Invention Was Made

(a) The Breadth of all of the Pending Rejected Claims 155-172 is Definite

The pending claims are drawn to a modified release tablet containing bupropion or a salt or enantiomer that is suitable for once-daily bupropion administration and which is "bioequivalent" to Wellbutrin® or Zyban/Wellbutrin® SR when administered once-daily. As defined in the application, and well known in the relevant drug formulation art, for a first

controlled release drug formulation to be bioequivalent to a second controlled release drug formulation according to FDA guidelines signifies that the 90% CI corresponding to the ratio of the geometric means of the AUC 0-inf; AUC 0-t and Cmax of these formulations ranges from 80-125%. Therefore applying this well accepted definition of bioequivalency to the claimed invention, a modified-release tablet according to the invention, in order to fall within the scope of the claims, must possess a 90% CI ratio of the geometric means of the AUC 0-inf; AUC 0-t and Cmax values to those of Wellbutrin® or Zyban/Wellbutrin® SR that ranges from 80-125%.

As noted during an interview with the Examiner of this application Applicants' definition of bioequivalency is consistent with and adopts well accepted FDA guidelines for evaluating modified-release tablet drug formulations and particularly is used by the FDA in determining whether a proposed new drug formulation is bioequivalent to an already existing approved formulation containing the same drug. In support of this fact the Appellants submitted to the Examiner herein and her Supervisor Examiner Woodward during prosecution a publication contained on the FDA website wherein these bioequivalency guidelines are described in detail. For the Board's edification this same publication is submitted as Exhibit to this Brief. (Exhibit 1, "Guidance for Industry Bioavailability and Bioequivalence Studies for Orally and Administered Drug Products- General Considerations",)

In the §112 second paragraph rejection the Examiner concludes that all of the pending claims 155-172 are indefinite since they define the subject bioequivalent compositions by reference to bupropion compositions which are referred to by the tradenames Wellbutrin® and Zyban/Wellbutrin® SR. The Examiner asserts that the claim scope is uncertain since there "[a]re no description(SIC) in the specification of the exact ingredients of Wellbutrin® and Zyban, which can change over time." Appellants respectfully traverse.

At the outset Appellants respectfully note that the specification in paragraphs [0002-0004] describes the recited Wellbutrin® and Zyban/Wellbutrin® SR compositions as respectively corresponding to a commercially available immediate release bupropion composition which is administered 3 or 4 times daily or a sustained release bupropion containing formulation which is administered twice daily. Additionally, the specification as-filed provides

Tables as well as Figures which are referred to in the examples that contain the AUC inf, AUC 0-t and Cmax parameters (PK parameters) for said Wellbutrin® and Zyban/Wellbutrin® SR compositions administered under these prescribed conditions. It is these PK parameters to which the modified-release tablet formulations according to the invention are bioequivalent according to the above-referenced and well recognized definition of bioequivalency in the relevant art (modified-release drug containing tablets) as evidenced by the FDA Bioequivalency Guidelines (Exhibit). Therefore, one of ordinary skill in the relevant art in possession of the as-filed application would readily understand that the reference to Wellbutrin® and Zyban/Wellbutrin® SR formulations in the context of the claimed invention necessarily refers to commercially available FDA approved immediate release or twice-daily sustained release bupropion containing formulations which possess AUC o-inf, AUC 0-t and Cmax values (PK parameters) as set forth in the Tables and Figures of this application. Accordingly, even assuming arguendo that such FDA approved, commercially available Zyban/Wellbutrin® SR or Wellbutrin® formulations were later modified (which they can not be absent express FDA authorization), the scope and meaning of the claims would still be clear from the teachings of the subject application including in particular the Tables and Figures which contain AUC and C_{max} parameters therefor.

Additionally, Appellants respectfully submit that the Examiner's concern as to the possibility of change of the recited bupropion formulations is misplaced since the FDA has approved the recited bupropion formulations for therapeutic usage in large part based on their PK parameters, i.e. the AUC 0-inf, AUC 0-t and Cmax parameters which are used to assess bioequivalency as these parameters define the drug levels of bupropion in the plasma including peak drug levels in the plasma over the dosing duration and drug plasma levels during the treatment regime. In fact these PK parameters are critical to safety and efficacy (as noted in paragraph [0004] of the subject application) since maintaining bupropion drug levels at defined levels in the blood after administration is imperative as a sudden surge of bupropion in the blood (which e.g., sometimes occurs with previous immediate release bupropion formulations) may result in seizure. Therefore, contrary to the Examiner's concern, the commercially available Wellbutrin® and Zyban/Wellbutrin® SR formulations which are recited in the claims, which

were approved by the FDA for usage in treating depression or smoking cessation, are not subject to change and in fact cannot not be changed without the manufacturer thereof (GlaxoSmithKline) obtaining the FDA's express approval (because of underlying public safety and efficacy issues).

The facts herein can be contrasted with other trademark or tradename products in commercial usage which are not subject to stringent government regulation and which therefore are potentially subject to change over time. Appellants respectfully submit that the facts herein are non-analogous to those in the cited Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982)

Indeed, because of the anticipated invariant nature of the recited Wellbutrin® and Zyban/Wellbutrin® SR bupropion drug products which have obtained FDA approval for treating depression and smoking cessation and which have been in wide usage for a number of years, Appellants respectfully submit that defining the subject modified release tablets by reference to these tradenames actually more precisely defines the scope of the claimed invention than if the exact ingredients of these bupropion formulations were recited as suggested by the Examiner. With respect thereto, it is telling that the FDA bioequivalency guidelines (Exhibit) define bioequivalency based on AUC and Cmax values (PK parameters) and not by the exact constituents contained therein such as stabilizers, lubricants, and other excipients since it is well understood by those skilled in the art that many of such constituents may be varied while still obtaining a bioequivalent composition exhibiting the desired PK parameters required for safety and efficacy. In other words, the instant claims are directed to bioequivalence to the pharmacokinetic parameters of the Wellbutrin and Zyban/Wellbutrin SR products, not their structural constituents. Those pharmacokinetic parameters are set forth in the specification and therefore are not subject to change.

(b) The §112 Second Paragraph Rejection of Claims 165-167 Especially Cannot Be Maintained Because These Claims Recite PK Parameters Which Define Bioequivalent Modified Release Formulations According to the Invention

Based on the foregoing, Appellants respectfully submit that the §112 second paragraph rejection should not be maintained against any of claims 155-172 since (i) the meaning of the recited Wellbutrin® and Zyban/Wellbutrin® SR formulations and their inherent PK parameters upon in vivo administration (which define bioequivalent compositions encompassed by the claims) would be clear to an ordinary artisan from the as-filed specification including the Tables and Figures; and (ii) and further because the recited Wellbutrin® and Zyban/Wellbutrin® SR tradename drug formulations, because they correspond to well known, readily available FDA regulated trademarked compositions (and which have been commercially available unchanged for a number of years; Wellbutrin® was approved 18 years prior to the earliest filing date of the subject application and Zyban and Wellbutrin® SR waere approved 16 and 17 years prior to the earliest filing date of the subject application) , are not subject to change, therefore the recitation of these Tradenames actually renders the claims of much more precise scope than if the Patent Office required Appellants to remove such phraseology from their claims in lieu of "structural phraseology" as suggested by the Examiner.

However, assuming *arguendo* that the Patent Office declines to accept these arguments, Appellants respectfully submit that the §112 second paragraph rejection at least cannot be maintained against dependent claims 165-167 since these claims explicitly recite specific AUC and Cmax parameters possessed by bioequivalent modified release compositions encompassed by these dependent claims. Therefore, the meaning of these dependent claims and the bioequivalent bupropion tablet formulations claimed therein does not implicate the definition of the tradename bupropion compositions recited in claim 155 from which these claims depend.

3. Summary

Appellants respectfully submit that the §112 second paragraph rejection of claims 155-172, or at the least claims 165-167, should be reversed since the recitation of the Tradenames for the specific FDA approved bupropion compositions in Claim 155 does not render these claims of indeterminate scope since (1) the meaning of these Tradename bupropion formulations is clear from the subject specification (2) even if it were not these bupropion

formulations are in the public domain and were as of the date of invention and are not subject to significant change because of safety and regulatory factors; and (3) the dependent claims 165-167 explicitly recite the PK parameters which define bioequivalency and therefore the scope and meaning thereof does not involve the definition of the recited Tradename bupropion formulations. Accordingly, Appellants respectfully submit that the indefiniteness rejection under 35 U.S.C. §112 of claims 155-172 should be withdrawn.

B. The Rejection of Claims 155-172 Based on Alleged Inadequate Written Description Is Improper and Should Not Be Sustained

The Examiner has also rejected claims 155-172 under 35 U.S.C. §112, first paragraph, alleging that the specification does not provide adequate written description of the claimed invention. The Office Action asserts that the claimed invention is rejected because:

"they do not identify the structure, material, or acts set forth in the specification that would be capable of carrying out the functional properties recited in the claims. It appears from the specification that the claimed bioequivalent is achieved from formulation that contains specific structure, such as dosage core with coating layers that comprise specific ratios of film forming polymers (pages 18-19 and 21; examples 1 and 2). This is also evident by the comparison data showing formulations with different structure that resulted in different functional properties (see comparative example 8)."

Appellants respectfully traverse the rejection and submit that the rejection is improper.

1. Standard for Written Description

According to the MPEP, to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. Possession of a claimed invention may be demonstrated by description of the invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. MPEP §2163 I. Moreover, a strong

presumption exists with regard to originally filed claims that an adequate written description of the claimed invention is present when the application is filed. MPEP §2163 I.A.

Case law indicates that structural features of a claimed invention are important for satisfying the written description requirement. The Federal Circuit in *Fiers v. Revel*, 25 USPQ2d 1601 (Fed. Cir. 1993), stated that an adequate written description "requires a precise definition, such as by structure, formula, chemical name, or physical properties." *Fiers*, 25 USPQ2d at 1606. The requirement for written description of a chemical genus is further set forth in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). As described by the Federal Circuit in *Lilly*, "[a] description of a genus of cDNAs may be achieved by means of . . . a recitation of structural features common to the members of the genus . . . ." *Lilly*, 43 USPQ2d at 1406.

Moreover, proper description of functional features of a claimed invention can also satisfy the written description requirement. For example, in *Enzo Biochem, Inc. v. Gen-Probe Incorporated*, 63 USPQ2d 1609 (Fed. Cir. 2002), the claimed polynucleotide sequences in the patent in question were defined based on their ability to differentially hybridize to reference polynucleotide sequences from deposited bacteria *N. gonorrhoeae* and *N. meningitidis*. The Federal Circuit held that this hybridization function-based description may, in some cases, satisfy the written description requirement because of "a complementary structural relationship" between the claimed sequences and the reference sequences. *Enzo*, 63 USPQ2d at 1616. The Federal Circuit further stated that "*Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 USPQ2d 1385, 1398 (Fed. Cir. 2003). These cases support a view that the claims need not specify a recited structure to satisfy §112 written description even in an art (recombinant DNA) more unpredictable than herein (drug formulation technology).

2. Appellants Specification Establishes That They Were in Possession of The Claimed Invention As Defined by the Recited Structural and Functional Features and Moreover Would Place the Ordinary Skilled Artisan in Possession of Modified-Release Tablets According to the Claims

The present invention for the first time provides controlled-release bupropion formulations that are suitable for once-a-day administration and which are bioequivalent to previous immediate release or sustained release bupropion formulations (Wellbutrin® or Zyban/Wellbutrin® SR). Based on these properties the subject invention alleviates inherent safety disadvantages of prior commercially available bupropion compositions because the subject once-a-day formulation, given its modified- release profile over a 24 hour dosing period, is less prone to causing seizure in susceptible individuals. Moreover, because the subject bioequivalent controlled release tablets are only administered once daily and do not exhibit a food effect these tablet formulations significantly simplify patient compliance thereby potentially enhancing efficacy in individuals being treated for depression or smoking cessation who are being prescribed bupropion. This is a significant advantage given the adverse consequences sometimes associated with untreated depression including obesity, sleeping irregularities, and most tragically suicide.

In fact based on the substantial and well recognized advantages of bioequivalent once-a-day bupropion compositions as claimed herein, vis-à-vis previous bupropion tablet formulations that require repeated dosing, once-a-day modified release bupropion tablets (that are bioequivalent to immediate release Wellbutrin® and Zyban/Wellbutrin® SR tablets), and which correspond to all of the claims on appeal herein, and the tablets exemplified in the subject application, obtained FDA approval on August 28, 2003 and are being sold by Glaxo Smith Kline under the Tradename Wellbutrin® XL. These once-a-day bioequivalent modified release tablets presently account for over 60% of total bupropion sales and generate over 1 billion dollars in total revenues annually (see Exhibit submitted to the Patent Office at the interview dated May 31, 2006) (Exhibit). In addition as noted therein and as discussed at the Examiner

interview dated May 31, 2006 these annual revenues and relative market share are still on the rise.

As noted above, the Examiner has rejected all of claims 155-172 on the basis that the claims do not satisfy the written description requirement since "they do not identify the structure, material, or acts set forth in the specification that would be capable of carrying out the functional properties recited in the claims." Appellants strenuously disagree.

At the outset, Appellants respectfully submit that the specification clearly establishes that Appellants were in possession of bioequivalent modified-release tablets possessing the structural and functional properties recited by the claims and moreover that the teachings of the specification taken in view of the state of the relevant prior art in existence at the time of the invention would place a skilled artisan in possession of bioequivalent modified release tablets according to the claims.

However, prior to traversing this rejection on Appeal herein Appellants summarize below the prosecution history of this application, and particularly the recent interview, as it is believed to be relevant to the issues under consideration. Particularly, by way of background Appellants note that this application was accorded special status based on a granted Petition to Make Special. This Petition was submitted in order to expedite allowance and obtain grant of claims that would adequately protect Appellants' invention because of the tremendous commercial importance of this invention to the subject Assignee Biovail Laboratories International SRL (BLIS) (a wholly owned subsidiary of Biovail Corporation) and because of pending litigations relating to the subject matter pursued herein. (Appellants note that within about one year after the FDA approval of a once-a-day bupropion modified release tablet formulation according to the invention on August 28, of 2003 that 4 different generics have submitted ANDA applications for once-a-day bupropion modified release tablet formulations that are alleged to be bioequivalent to those claimed herein).

Based thereon, in order to expedite allowance promptly after receipt of the initial Office Action the undersigned along with representatives from the Assignee (BLIS). had an

initial personal interview with then-Assistant Examiner Tran and now Primary Examiner Tran. During this interview the present claims were submitted as an exhibit and the patentability of these claims over the then-cited prior art was discussed. Particularly, it was explained how these claims were believed to be free of the previous prior art rejections which did not teach a bioequivalent once-a-day bupropion modified release as claimed herein. In support of these arguments the undersigned relied on comparative data in the subject application. At no point during the interview did the Examiner suggest that these claims might raise §112 written description or enablement issues. Nor did the Examiner criticize the comparative data distinguishing the prior art (Seth US Patent 6,143,327). In addition at no point during the interview did the Examiner remotely infer that the claims discussed at the interview would not be entered on formal submission. In fact she indicated that she would consider their patentability on formal submission.

Because of the special status of this application, the claims presented at the interview were formally submitted along with a substantive response on April 4, 2006, very shortly after the first Examiner interview. Because of the special nature of this application and its great importance to the Assignee BLIS when they had not received any action on the claims and the response submitted on April 4, 2006 as of mid-May, on the Assignee's instruction the undersigned contacted Examiner Tran by telephone and was advised that the claims submitted in the April 4, 2006 Reply would not be entered on the basis that they were directed to a patentably distinct invention than the claims originally submitted. The Examiner further indicated that non-entry was at the direction of her then-Supervisor Examiner Thurman Page and that a one-month non-responsive letter would soon be mailed. This position (non-entry) was immediately taken up with the Examiner's then-Supervisor Examiner Page to no avail and the undersigned was advised by Supervisory Examiner Page to take this issue up with the Group Director. Thereupon, the undersigned contacted the Director of the Group Bruce Kisliuck and was later informed by Examiner Tran that the claims would be entered and that Examiner Tran was being re-assigned to a new Supervisor Examiner Michael Woodward. The undersigned shortly thereafter contacted Examiner Tran to schedule a second interview since it was apparent from the telephone

conversation that her new Supervisor would be the primary decision maker in this application. Initially this interview was declined, but Examiner Woodward later graciously changed his mind and granted the interview after the undersigned telephoned him and explained that the subject matter covered by the application at issue related to 4 ongoing litigations the outcome of which potentially would have tremendous financial and personal impact to the Assignee of this application.

This interview was held on May 31, 2006 and was attended by Salim Mamajiwalla, Director of Intellectual Property from Biovail Corporation, as well as Michel Chouinard, Chief Operating Officer of BLIS, the undersigned and Examiner Tran and Examiner Woodward. At the interview Appellants' representatives explained how the development of the subject once-a-day bupropion modified-release bioequivalent tablet product had taken many years of research and clinical development and involved substantial financial expenditures by Biovail. Particularly, it was noted that as part of the development of this product that Biovail acquired technology and underlying patents relating to bupropion modified release tablets from another company PharmaPass for several hundred million dollars which company was eventually acquired by Biovail. It was noted that this acquisition included the delayed release bupropion tablet technology patented in US Patent No. 6,143,327 (cited in the initial Office Action dated December 7, 2005 as allegedly anticipatory prior art against the original claims). It was also discussed that even with the know-how obtained from PharmaPass that the development of the subject bioequivalent once-a-day modified release tablets still required considerable additional research and clinical development as evidenced by the fact that FDA approval of a modified-release tablet as claimed herein did not occur until August 28, 2003, i.e., about 5 years after the effective filing date of the acquired PharmaPass patent (US Patent No. 6,143,327 now assigned to Biovail). Appellants further noted that the original innovator of bupropion, GlaxoSmithKline, was apparently unable to develop a bioequivalent bupropion modified release tablet as claimed herein and that based thereon entered into an exclusive license arrangement with Biovail relating to the once-a-day bupropion technology claimed herein.

Appellants further noted during the interview that the FDA approved product which is described herein and which is marketed by GlaxoSmithKline constituted a substantial advance over previous bupropion medicaments because it was and still remains the only FDA approved once-a-day bupropion tablet. Moreover, it was emphasized that while the development of the subject bioequivalent modified-release tablets claimed herein required a number of years of research and clinical development as well as substantial financial investment by the company, that once this modified-release tablet was commercialized by Biovail (and the subject patent application published by the USPTO on its website) that a number of generic competitors (4) within about a year of Biovail's obtaining FDA approval to market Wellbutrin® XL have submitted ANDA applications directed to once-a-day modified release tablets purportedly bioequivalent to Wellbutrin® XL which is the commercial embodiment of the invention claimed herein.

With respect thereto, Appellants explained that while the initial development of a bioequivalent drug formulation is often complex, unpredictable and time consuming as it was herein, that once one is developed it often is relatively easy for a generic to"reverse engineer" the product and also to modify the formulation while retaining the desired bioequivalency. Based thereon, it was argued strenuously that claims that cover modified-release tablets possessing the recited bioequivalent properties should be granted since the subject application does sufficiently enable and describe to a skilled artisan how to make once-a-day administrable bioequivalent modified release tablets as claimed herein.

Further during this interview the prior art then of record was discussed and it was explained that the cited prior art (US Patent No. 6,143,327) failed to exemplify a bioequivalent once-a-day bupropion formulation as claimed herein. The Appellants' representatives referred to comparative data in the present application (Example 8) substantiating this fact and noted that the control-release coat in the Seth modified-release tablet discussed in the '327 patent did not achieve bioequivalency apparently because of the ratio of the polymers contained in the control-release coating as well as the amount of the coating contained in the '327 patent tablet formulation.

During the interview the Examiners queried the Appellants as to the definition of "bioequivalent" and suggested that this term was ambiguous. Appellants' representatives explained that this term is well understood in relevant drug formulation art, particularly controlled release tablets as claimed herein, and referred to the definition of bioequivalency in the subject application which adopts FDA guidelines for bioequivalent controlled release drug formulations. Appellants also offered to further factually establish the well accepted nature of this definition of bioequivalency by submission of the FDA guidelines for bioequivalency from the FDA website. These FDA bioequivalency guidelines were e-mailed to the Examiners as a PDF the same day of the interview. (Exhibit)

Finally, during the interview Supervisor Examiner Woodward and Examiner Tran graciously indicated that they were in agreement that there was allowable subject matter in the subject application. However, they advised that they would need to assess the scope of allowable subject matter. Examiner Woodward further indicated that they would advise Appellants' attorneys as to the scope of allowable subject matter prior to issuing a subsequent Office Action and within several days of the interview held on May 31, 2006. Unfortunately, this did not happen. Rather, a final rejection was mailed on July 14, 2006 prior to Appellants being given an opportunity to place the claims in condition for allowance. The suggestion therein as to the scope of allowable subject matter indicates that the Examiners would be willing to allow a claim containing the "limitations of claims 129, 28 and 45 and/or 47 as originally filed".

It can be clearly seen upon review of Claim 129 limited further with the limitations of claims 28, 45 and/or 47 that the suggested allowable claim is extremely narrow in scope. Indeed this claim spells out all the excipients in the exemplified tablet formulation as well as the weight percentages thereof. Because of the finality of the rejection, and the unacceptable nature of the proposal to the Assignee (because this claim in no way adequately protects Appellants' invention), and further based on the fact that the outcome of this application may implicate the outcome of several ongoing litigations, Appellants were left with no choice except to appeal the outstanding rejections in the hope that the Board of Appeals will adopt a more reasonable stance.

Turning now to the written description rejection, the claims are rejected on the basis that the specification would not reasonably convey to one of ordinary skill in the art that Appellants were in possession of the claimed invention at the time the application was filed. The Examiner asserts that it "appears from the specification that the claimed bioequivalent is achieved from formulation that contains specific structure, such as dosage core with coating layers that comprise specific ratios of film forming polymers (pages 18-19 and 21; examples 1 and 2). This is also evident by the comparison data showing formulations with different structure that resulted in different functional properties (see comparative example 8)."…. Accordingly, the structure which makes up the formulation must be clearly positively specified".

Based on this statement of the rejection and the indication of the scope of allowable subject matter in the Final Office Action it is Appellants' understanding that the Examiner has concluded that the invention as described in the as-filed specification is limited to modified-release tablets comprising:

(i) a core containing a precise combination of excipients such as binders and lubricants as set forth in now cancelled claim 129; and which is surrounded by;

(ii) a modified-release coating and a moisture barrier that are comprised of the exact polymeric constituents and relative amounts thereof as recited in claim 129, and claims 28, 45 and 47.

Appellants respectfully disagree. Rather, it is clear from the as-filed specification that the inventors understood that their invention is more broadly directed to and indeed provides for the first time modified release tablets that are bioequivalent to Wellbutrin® and Zyban/Wellbutrin® SR (sustained release) tablets. This is apparent for example from paragraph [00016] and [00017] of the specification which state that "the present invention relates to a modified-release tablet of a pharmaceutically acceptable salt of bupropion, preferably bupropion hydrochloride.

This is further clear from the inventors' statement in the application that "the advantage of the modified-release tablets of the invention not afforded by the prior art

commercially available Wellbutrin® or Zyban/Wellbutrin® SR tablets is that the subject modified-release tablets allow for a once daily administration regimen, is bioequivalent to the commercially available prior art tablets, and do not exhibit a food effect". Therefore, in the originally filed patent application, the present inventors clearly established their belief that they were in possession of an invention having the essential features set forth in independent claim 155 and those dependent thereon.

With respect thereto, Appellants respectfully submit that it would be readily understood by a skilled artisan, in possession of the specification, that the claimed modified-release medicament as set forth in Claim 155 is directed to a medicament in the form of a tablet that comprises bupropion and a substrate (such as a control-release coat) which regulates and provides for the controlled release of the bupropion from the tablet such that drug release on once-daily administration is bioequivalent to that of Wellbutrin® or Zyban/Wellbutrin® SR tablets. This would be clear in part from the explicit wording of the claim which is directed to a modified-release tablet that is bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR construed in view of the exemplified modified-release tablet drug formulations as well as the definition of "modified-release" drug formulations contained in this application.

With respect thereto, Appellants note that the subject application describes and exemplifies in the examples the preparation of several modified-release tablet formulations according to the invention that possess bupropion and a material (control-release polymeric coating) which substantially regulates bupropion release which are bioequivalent to Wellbutrin® and Zyban/Wellbutrin® SR. Moreover the subject application contains the results of clinical testing which demonstrates unequivocally that these modified tablets are indeed bioequivalent to Wellbutrin® and Zyban/Wellbutrin® SR and further do not elicit a food effect, i.e., they are bioequivalent when taken once daily in the presence or absence of food. As noted, supra, modified-release tablet formulations according to the invention are now commercially available under the Tradename Wellbutrin® XL.

Appellants further acknowledge that the subject specification exemplifies several bioequivalent modified-release tablets that all possess a bupropion containing core structure containing specific constituents including the bupropion drug, binder and lubricant, which core is surrounded by a polymeric control-release coating (material that substantially regulates drug release) as well as a moisture barrier also comprised of polymers (that enhances drug stability during storage). However, Appellants respectfully submit that the Appellants' claims should not be relegated to the very specific substituents contained in the exemplified embodiments. To do so would be improper since it fails to take into account the high level of requisite skill in the art and the more generic nature of the invention.

A skilled artisan, in possession of the teachings provided by this application, would be well aware that the specific excipients in the core of the subject modified release tablet may be modified without adverse effects to the desired bioequivalency properties. In fact, the core constituents in the exemplified modified-release tablets, other than the bupropion drug, do not significantly affect the release of the drug from the modified release tablet. Rather the desired modified release of bupropion is achieved substantially by the presence of a material (modified-release coating) surrounding the bupropion comprising core. Based thereon, the Examiner's indication of the scope of the subject matter that is allegedly free of the §112 written description rejection (a claim containing the limitations of claims 129, 28 and 45 or 47 construed together) is entirely unreasonable since it would be understood by a skilled artisan that many of the additives and excipients in the tablet formulation recited in Claim 29, and the amounts thereof, would not be essential to the claimed invention since they would not be anticipated to significantly affect bupropion drug release from the modified-release tablet.

Moreover, based on the teachings of this application it would be routine for a skilled artisan to modify the particular constituents in the exemplified bupropion containing drug core as well as the amounts thereof and to select for other modified-release tablets that retain the desired bioequivalency properties. In fact the subject specification in paragraph [00065] explicitly teaches that the core of the inventive modified-release tablet "contains conventional excipients". Moreover, in paragraphs [0067]-[0072] the specification would further

place a skilled artisan in possession of a range of different excipients including a variety of well known binders and lubricants which may be substituted or admixed with the bupropion containing core of the exemplified modified release tablets without anticipated adverse effects to the desired release properties of the modified-release tablets. The fact that the core constituents are not essential to drug release is apparent further from paragraph [0070] of the subject application which discloses that the bupropion comprising core in the modified-release tablets functions as "an immediate release formulation". This clearly would convey to a skilled artisan in the relevant drug formulation art that the core constituents in modified-release tablets according to the invention may be varied without significant impact on the claimed invention since they do not significantly impact the desired modified release and therefore were not regarded by the inventors to constitute an essential aspect of the invention.

Turning now to the Examiner's apparent other concern, i.e., that the claims do not place one skilled in the art in possession of a modified-release tablet as disclosed because the claims fail to recite the "coating layers that comprise specific ratios of film forming polymers", this also is respectfully traversed. With respect thereto, Appellants concede that the subject specification only exemplifies 2 bioequivalent bupropion tablet formulations that respectively contain 150 or 300 mg of bupropion, and which each further respectively comprise (i) a control-release coating that substantially controls bupropion drug release as well as (ii) a moisture barrier coating that impedes moisture retention, wherein both coatings are comprised of specific polymeric constituents comprised in specific weight percentages. However, notwithstanding Appellants respectfully submit that the teachings of the invention would place a skilled artisan in possession of the invention as generically set forth in Claim 155 and the claims dependent thereon.

At the outset, Appellants respectfully note that the subject specification clearly teaches that the function of the moisture barrier is to preclude moisture from coming in contact with the hygroscopic bupropion. This is clear e.g., from paragraph [0014] of the specification wherein the "moisture barrier" is defined as well as Example 2 which provides dissolution data demonstrating that this moisture barrier coating does not function as an enteric coat. Therefore,

it is apparent from the specification that the function of this coating is to enhance the stability of the bupropion contained in the subject modified release tablets. Indeed, this is the reason that only some of the claims on appeal specify the degree of bupropion stability under specific relative humidity and temperature conditions since this is the result of the presence of the moisture barrier and is not essential to the invention as set forth in claim 155. Therefore, it would at least be clear to a skilled artisan from the teachings of this application including Example 2 that the possession of a modified release tablet possessing the bioequivalency properties required by Claim 155 would not be anticipated to require the presence of a moisture barrier.

Turning now to the control-release coating, Appellants respectfully submit that it would further be apparent to a skilled artisan in possession of the specification that the subject modified-release tablets necessarily comprise a material , e.g., a control-release coating that regulates modified release otherwise the drug would not be delivered by modified release and the recited bioequivalency over a 24 hour dosing period would not be achieved. Accordingly, a reasonable claim construction requires that claim 155 be construed to include the presence of some substrate, e.g., a modified release coating that modulates release over a 24 hour period irrespective of the fact that this is not explicitly recited.

Appellants further respectfully submit that the teachings of the subject application adequately establish that (i) the inventors were in the possession of and further would place one skilled in the art in possession of appropriate materials i.e., control-release coatings that would yield modified release tablets as claimed herein, particularly modified-release tablets which are bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR and (ii) that the invention is not limited to modified release tablets comprising the specific modified release coating and the amounts therof contained in the two exemplified modified-release tablets.

To the contrary, the subject application particularly describes that the substrate that modulates drug release, i.e. the control-release coating may contain a variety of possible water insoluble water impermeable film forming polymers, water soluble polymers, and

optionally plasticizers and further that these amounts may be varied in order to achieve the desired drug release rate (see paragraphs [0075]-[0083] of the subject application.). Therefore, the disclosure is very clear that these constituents may be varied.

Therefore notwithstanding the fact that in the exemplified embodiments that the control-release coating comprises ethyl cellulose as the film-forming polymer, polyethylene glycol 1450 as the plasticizer, and polyvinyl pyrrolidone as the water soluble polymer it would be readily understood by a skilled artisan that is exemplary and that other control-release coatings may be substituted therefore. Also, as correctly pointed out by the Examiner while the application further teaches in paragraph [0080] that a preferred ratio of the film forming polymer:plasticizer:water soluble polymer for a 150 mg bupropion modified release tablet may vary from 3:1:4 to about 5:1:3 and preferably is 4:1:3 and that for a 300 mg dose the same ratio preferably ranges from 7:2:6 to about 19:5:18 and more preferably is 13:4:12 it would be anticipated that such ratios also may be readily varied by one of ordinary skill in the art, e.g., if different polymers are used in the control-release coating while still maintaining the unique PK parameters of the claimed invention.

As previously mentioned, the subject specification in paragraphs [0077-0081] exemplifies a wide range of different film-forming polymers, plasticizers and water soluble polymers that may be substituted for those contained in the exemplified control-release coatings. In addition, the subject specification teaches in paragraph [0082] that "the permeability of the control-release coating may be varied by altering the ratio of the water-insoluble, water permeable film-forming polymer: water soluble polymer and/or the amount of coating applied to the tablet core".

Appellants respectfully submit that based on these teachings it would be apparent to a skilled artisan in possession of this application that the polymeric constituents contained in the control-release coating which is comprised in the subject modified release tablet may be varied, as well as the relative amounts thereof or the total amount of the coating and that

modified-release tablets selected possessing the desired bioequivalent properties upon once-daily in vivo administration.

The fact that Appellants' invention should not be limited to specific polymer combinations or ratios or amounts thereof is further supported by the fact that the ratios and relative amounts of the polymers contained in the control-release coating vary substantially between the exemplified 150 and 300 mg bioequivalent bupropion compositions. This may be seen from Table 3 of the subject application. Hence there is convincing experimental proof in the as-filed application that the composition of the control-release coating (ratios of polymers contained therein) as well as the amount of this coating may be varied while still obtaining modified-release tablets that are bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR when administered once-daily.

With respect thereto, the Examiner supports her position that the application allegedly only provides written description support for control-release tablets comprising the exemplified control-release coatings based on the comparative data in Example 8. Particularly, she correctly points out in the final rejection that Example 8 of this application contains comparative data revealing that a prior art bupropion modified- release tablet formulation (disclosed in US Patent No. 6,143,327 (Seth patent)), which contained a control-release coating comprising the same polymers, but in different ratios and weight percentages as the exemplified embodiments of the invention, was not bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR. The Examiner is of the view that this comparative data demonstrates that the invention should be restricted to the exact particulars of the exemplified operative embodiments. The position of the Examiner is respectfully traversed.

This comparative data contained in the subject application was provided in order to illustrate that the closest prior art to the claimed invention does not exemplify a once-daily modified release tablet that is bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR as claimed herein. This comparative data was provided in order to preempt a potential prior art rejection based on this patent and expedite grant. Moreover, the comparative data was readily

available based on the fact that this patent and the underlying technology and know-how disclosed in the '327 Patent was acquired by BLIS. However, this comparative data does not support a view that Appellants are not entitled to claims of the current scope based on inadequate written description.

By contrast, the instant application places one skilled in the art in possession of the claimed invention as it provides convincing data, based at least on the exemplified 150 and 300 mg bupropion tablet formulations, which establish that bioequivalent control-release tablets possessing the desired bioequivalency can be obtained using control release coatings having different polymeric composition as well as different coating amounts. Particularly, it can be seen from Table 3 of this application that the exemplified 150 and 300 mg tablets, while both bioequivalent, contain different ratios of polymers in the control-release coating and further contain different amount of such control-release coating. This data supports a conclusion that Appellants' claims should not be restricted to modified release tablets containing the exemplified control release coatings or amounts therof since such ratios and amounts may be varied while retaining the desired bioequivalency. Indeed, the comparative data based on the formulation in the Seth patent provides the skilled worker further guidance as to which combination of core and polymers will yield a bioequivalent formulation and which will not.

Thus, based on the foregoing, Appellants respectfully submit that the requisite structural and functional features commonly shared by all members of the claimed genus of modified-release tablets have been described in detail, which would "clearly allow persons of ordinary skill in the art to recognize that [the applicant] invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991).

3. The Genus Of Modified-Release Tablets Claimed Have Well Defined, Readily Verifiable Structural and Functional Features

Appellants in addition wish to emphasize that the claimed subject matter of this invention relates to modified release tablets that possess specific drug release properties that can readily be identified using known methods such as are described in this application. Essentially,

one skilled in the art based on the teachings of this application would be placed in possession of the requisite information in order to determine whether a modified-release tablet possesses the desired bioequivalent properties in vivo when administered once-daily.

In particular, the subject application discloses the precise dissolution characteristics of the exemplified bioequivalent modified-release tablets as well as disclosing a range of different excipients and additives such as binders, lubricants, polymers and plasticizers which may be used in lieu of the specific constituents contained in the exemplified embodiments. Additionally, the specification teaches that the amounts thereof may be varied.

With respect thereto, it would be within the purview of a skilled artisan to practice the teachings of this application in order to produce different modified-release bupropion tablets containing from about 150 or 300 mg of bupropion, and to screen the produced modified-release tablets in order to select for those that possess in vivo PK parameters consistent with those of the exemplified bioequivalent modified-release tablets. .

It should be noted that Appellants' arguments are not inconsistent with arguments made at the recent interview as to the lack of predictability of a correlation between in vitro dissolution and in vivo pharmacokinetic parameters. Appellants maintain that in vitro dissolution of a modified-release tablet by itself cannot be correlated to drug release and bioavailability in vivo absent convincing in vivo data establishing such a correlation. This lack of predictability is even accepted by the FDA as evidenced by a publication contained on the FDA website submitted to the Examiner during prosecution of this application. (Exhibit) The subject application contains an abundant amount of clinical data establishing the desired in vivo properties exhibited by the exemplified modified release tablets. Given this and other teachings related to the structural and functional features of the claimed invention, Appellants respectfully submit that once such information is placed in the public domain it is well within the purview of the skilled artisan to design a once-daily formulation of bupropion hydrochloride that is bioequivalent to the currently marketed Wellbutrin® XL embraced by the instant claims being appealed. As explained above, and reiterated here, this is further evidenced by the fact that while it took several years for the Appellant to develop a successful once-a-day formulation of

bupropion hydrochloride that is bioequivalent to Wellbutrin® and Zyban/Wellbutrin® SR it only took a mere 14 months for not one (1), but four (4) ANDA filers to develop a formulation bioequivalent to Wellbutrin® XL, each of which is expected to be structurally different from one another as each was developed by a different company at different times in a highly competitive business environment.

Therefore, based on the foregoing, Appellants' disclosure would place a skilled artisan in possession of the genus of modified-release tablets embraced by the claims.

4. The Written Description Rejection Is Based on Improper Reasoning

Appellants further contend that the written rejection under 35 U.S.C. §112 is improper, because the Examiner's reasoning in support of the rejection is flawed. More specifically, the Examiner seems to allege that the claims encompass a disproportionately large genus of modified-release tablets, based on the comparative data in Example 8 and that Appellants were not in possession of the claimed invention. See paragraph bridging pages 2 and 3 of the Final Office Action.

Appellants respectfully disagree. MPEP §21633II.A.(a) (ii) explicitly states that "there may be situations where one species adequately supports a genus." This is such a situation based on the extensive written description in the application and the high level of skill in this art. Moreover, Appellants should be entitled to claims of the current scope, further since Appellants' disclosure exemplifies several modified-release tablet formulations that correspond to the genus of modified-release tablets encompassed by the claims, i.e., that are demonstrated to be bioequivalent to Wellbutrin® and Zyban/Wellbutrin® SR. Also Appellants' specification provides extensive description as to how the exemplified tablets may be varied, e.g., the application provides a large listing of potential excipients such as binders, lubricants, polymers, and plasticizers, as well as providing a predictable means for determining whether a modified-release tablet falls within the scope of the claimed invention e.g., based on whether it possesses an in vitro dissolution profile consistent with those of the exemplary embodiments and the desired PK parameters consistent with bioequivalency.

In addition, Appellants respectfully submit the rejection is unsustainable because the Examiner has not met her burden of establishing why this specification would not place a skilled artisan in possession of modified-release tablets possessing the recited bioequivalency properties.

5. Summary

Based on the foregoing, Appellants believe that the written description rejection under 35 U.S.C. §112 is improper and should be withdrawn.

C. The Rejection for Lack of Enablement Is Improper

The Examiner has also rejected claims 155-172 under 35 U.S.C. §112, first paragraph, alleging that the claimed invention is not sufficiently enabled. The Final Rejection states that "the claims lack the description of the possible genus with the recited functional characteristics" Appellants respectfully traverse the rejection and submit that the rejection is unsustainable and moreover is unsubstantiated.

At the outset, Appellants respectfully submit that the Examiner has not met her burden in setting forth a proper prima facie enablement rejection. In fact the only statement of the rejection, i.e., that "the claims lack the description of the possible genus with the recited functional characteristics" would suggest that the Examiner intended to make a written description rejection rather than an enablement rejection. The written description rejection is addressed supra and the rebuttal arguments would seem to fully address the subject "enablement" rejection as articulated in the Final Rejection.

Assuming arguendo that an enablement rejection was intended to have been made, Appellants respectfully submit that it can not be sustained based on the present record. Indeed, the Final Rejection enumerates no reasons in support of her position that a skilled artisan could not practice the invention as set forth in the claims absent undue experimentation. Also, the rejection is further unsustainable since the Office Action fails to even concede the fact that

the subject specification exemplifies several working embodiments which possess all the recited limitations of claims 155-172 or why these working examples coupled with the extensive and detailed specification would not enable one skilled in the art to practice the invention as recited in Claims 155-172. Rather the rejection simply consists of a conclusonary statement that is totally unsubstantiated by appropriate scientific or legal reasoning.

1. Standard for Enablement

According to the MPEP, to satisfy the enablement requirement, the information contained in a patent specification must be sufficient to inform one skilled in the relevant art how to both make and use the claimed invention. MPEP §2164. Whether the enablement requirement is met depends on whether undue experimentation is necessary for one of skill in the art to practice the invention in light of the disclosure. MPEP §2164.01.

As set forth by the Federal Circuit in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), multiple factors should be considered when determining whether any necessary experimentation is undue. These factors include:

(a) the breadth of the claims;
(b) the nature of the invention;
(c) the state of the prior art;
(d) the level of one of ordinary skill;
(e) the level of predictability in the art;
(f) the amount of direction provided by the inventor;
(g) the existence of working examples; and
(h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Furthermore, to reject a claim for lack of enablement, the Examiner must carry the initial burden to establish a reasonable basis for questioning the enablement provided by the specification. MPEP §2164.04. Herein the Examiner has not met her burden since no reasonable scientific or legal basis has been provided in support of the enablement rejection. The

mere statement that the claims "lack the description of the possible genus with the recited characteristics" does not substantiate a conclusion that the skilled artisan could not produce bupropion containing modified-release tablets having the recited bioequivalency based on the teachings of the application and the state of the art at the time of the invention.

Rather, a proper rejection must apply the criteria set forth in Wands. The subject claims are enabled applying these factors at least for the reasons set forth below.

2. No Undue Experimentation Is Necessary to Practice the Claimed Invention

(a) The Breadth of the Claims

The pending claims are drawn to a modified release tablet comprising bupropion suitable for once-daily bupropion administration that possesses specific PK parameters in vivo, i.e., it is bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR when administered once-daily to a patient in need thereof. As noted above, in the rebuttal of the written description rejection, it would be apparent to a skilled artisan construing the claims that the invention in its broadest claimed embodiment as set forth independent claim 155 is directed to a modified release tablet comprising bupropion and a material that provides for modified release of bupropion therefrom, e.g., a control-release coat, such that the release of bupropion therefrom results in a tablet that is bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR when administered once daily. This would be apparent from the exemplified modified-release tablets as well as the definition of modified release forms in the subject application and the teachings of the specification taken as a whole.

The dependent claims which all depend from claim 155 further provide for the modified release tablet to be free of food effects, i.e., to be bioequivalent when administered in the presence or absence of food, to be stable under specific relative humidity and temperature conditions as set forth in the claims; to comprise specific amounts of bupropion (150 or 300 mg), as well as the use thereof for treating depression. Additionally, dependent claim 172 explicitly provides that the claimed bioequivalent modified release tablet comprise a bupropion containing core which is surrounded by a polymeric control-releasing coat which is in turn surrounded by a

moisture barrier coat that precludes moisture from coming into contact with the bupropion containing core.

Appellants respectfully submit that a skilled artisan, in possession of the subject specification would be able to practice the invention as set forth in claim 155 and all the claims which are dependent thereon. Indeed the working examples provide evidence of this fact since they describe modified-release tablet formulations that meet all the limitations of the claims. With respect thereto, Appellants concede that the claims are not restricted to the specific excipients and modified-release coating contained in the exemplary embodiments. However, Appellants submit that based on the teachings of this application (which describes for the first time and exemplifies in the form of at least 2 working embodiments once-daily bupropion tablet that possess the recited bioequivalent properties) that a skilled artisan would be able to vary the excipients and constituents therein, e.g., the particular polymers contained in the modified release coat and select for modified release tablets which are bioequivalent in vivo to the claimed invention. This experimentation would not be undue especially based on the fact that this disclosure precisely describes exemplary embodiments and teaches all the constituents thereof as well as teaching the exact in vitro dissolution characteristics of these exemplary embodiments. That this experimentation is not undue is further evidenced by the significantly short period it took for the four (4) ANDA filers to generate formulations bioequivalent to Wellbutrin® XL.

With respect thereto, it is noted again that this argument is not inconsistent with Appellants' arguments during prosecution that the in vitro dissolution of a modified release tablet by itself cannot be used to predict in vivo drug release. [In fact this argument was substantiated by a publication on the FDA website provided to the Examiner after the recent interview [Exhibit] which provides explicit guidelines for demonstrating whether there is a correlation between in vitro drug release and in vivo pharmacokinetic properties of the modified release formulation.]

Therefore, Appellants respectfully submit that a skilled artisan in possession of the teachings of the subject application would readily understand how to produce modified release tablets containing bupropion and further how to select for modified release tablets that

possess the disclosed in vitro dissolution characteristics with a reasonable expectation that modified-release tablets could be selected that possess the desired bioequivalent properties.

(b) The Nature of the Invention

As noted herein, the present invention relates to modified release tablets containing bupropion that are suitable for once-daily administration and which possess specific pharmacokinetic characteristics in vivo, i.e., they are bioequivalent to previous FDA approved bupropion medicaments, i.e., Wellbutrin® and Zyban/Wellbutrin® SR when administered once daily. As discussed in the subject application, prior to the present invention a modified release bupropion tablet suitable for once daily administration of bupropion was not commercially available much less a modified-release tablet that is bioequivalent to the prior immediate release or sustained release bupropion dosage forms. Additionally, prior to the present invention there were no once daily bupropion sustained dosage forms that were not subject to a food effect. Therefore, the present invention provides bupropion dosage forms that are improved because they simplify patient compliance because they only need to be administered once daily without concern about the time of administration relative to food intake.

The present disclosure exemplifies modified release tablets containing 150 and 300 mg of bupropion HCl wherein the bupropion is in an immediate release core and is surrounded by a control release coating and is also surrounded by a moisture barrier that precludes moisture from coming into contact with the bupropion core. Also the present application discloses in extensive detail the in vitro dissolution properties of these exemplified modified release dosage forms under conditions well accepted in the relevant art. Also, the specification establishes that the exemplified modified-release tablets are bioequivalent and are free of food effects based on clinical data contained in the examples and the tables and figures discussed therein. Based on these clinical results the exemplified 150 and 300 mg once-a-day tablet formulations disclosed in Examples 1 and 2 were approved for clinical use by the FDA on August 28, 2003 and are sold under the Tradename Wellbutrin® XL.

These teachings would enable one skilled in the art to practice the invention of claims 155-172 absent undue experimentation.

(c) The State of the Prior Art

Prior to the present invention the only available bupropion dosage forms required that the patient take the medication 3-4 times daily or twice daily. .

By contrast, prior to the invention once-daily modified release tablets containing some other drugs were known in the art as well as types of modified-release coatings useful therein. This is substantiated by prior art of record herein. Likewise the prior art was well aware of conventional excipients that may be incorporated in such once-daily modified release tablets such as binders, stabilizers, lubricants, and the like. Also, it was well known in the art that such excipients may be interchangeable with one another, e.g. one lubricant, binder, or stabilizer may be substituted for another. Therefore, one skilled in the art, in possession of the teachings of this application, and further familiar with the relevant pharmaceutical art, would readily understand as is disclosed in the subject application that one or more constituents in the exemplified bioequivalent modified-release tablets may be substituted with other similar excipients or that other excipients may be added without losing the desired bioequivalent properties upon in vivo administration. While Appellants acknowledge that not all modifications would be efficacious; the selection of operative modifications meeting the claim limitations would not rise to the level of undue experimentation. This application fully describes and enables the skilled artisan how to produce a modified release tablet meeting the limitations of all the claims absent undue experimentation.

Indeed, this application provides a very detailed disclosure and exemplifies in the form of several working embodiments how to produce and select modified dosage forms having the desired bioequivalent properties. A large body of literature pertaining to the preparation of controlled release drug formulations was in existence and in routine practice at the time the present invention was made. Thus, the prior art is in a highly advanced state.

(d) The Level of One of Ordinary Skill in the Art

The relevant research field of the present invention is pharmacology and drug formulation, where the substantive knowledge was abundant and the techniques were fully

developed, highly sophisticated, and routinely practiced among the artisans. In short, the ordinary level of technical skill in the relevant art was high. This further substantiates Appellants' arguments that the specification would enable a skilled artisan how to practice the invention absent undue experimentation.

(e) The Level of Predictability in the Art

The predictability in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. What is known in the art provides evidence as to the question of predictability. MPEP §2164.03. In the present case, the art was well aware at the time of invention that there is predictability that modified-release dosage forms may be modified e.g., by adding or varying different excipients without loss of bioequivalency. Therefore, absent evidence to the contrary it is reasonable to assume that a skilled artisan could extrapolate from the disclosed modified-release tablets how to produce other once-a-day administrable modified-release tablets that are bioequivalent thereto. Indeed Appellants' arguments are substantiated by the fact that 4 generics have filed Abbreviated New Drug Applications slightly more than about a year from Appellants obtaining FDA approval for the bioequivalent once-a-day bupropion modified-release tablets which are disclosed in the instant patent application. These four generic products derive from four different manufacturers and are made of various constituent elements, the only commonality being the presence of bupropion hydrochloride in the core and the alleged bioequivalence of each of the four to the tablets disclosed in the instant application.

(f) The Amount of Direction Provided by the Inventor

The present application provides ample direction for an artisan to practice the claimed invention. As such, a large amount of detailed direction is given in the present disclosure for practicing the claimed invention.

As noted, this specification describes in explicit detail how to produce modified-release tablets having the properties claimed herein. Also, the specification provides the precise in vitro dissolution properties thereof. Further, the specification describes various excipients and

additives which potentially may be modified or added to the exemplified modified-release dosage forms. Still further, the specification describes in detail the pharmacokinetic parameters to which a formulation must be bioequivalent. This information absent any evidence to the contrary would allow an artisan to practice the claimed invention absent undue experimentation.

(g) The Existence of Working Examples

This application provides several working examples that contain a very detailed description of bioequivalent modified-release dosage forms according to the invention. As discussed above the application describes and actually reduces to practice at least 2 modified-release tablets according to the invention. These working examples describe all the constituents thereof as well as the precise formulation conditions used to produce these tablets. Also, the specification further teaches the in vitro dissolution properties thereof under accepted conditions well known to those skilled in the drug formulation art. Still further, the specification further references and provides the results of extensive clinical studies which substantiate that these working examples, i.e. the described once-daily administrable modified release bupropion tablet dosage forms, exhibit the recited pharmacokinetic properties, i.e., they are bioequivalent to the prior bupropion dosage forms and are free of food effects when administered once daily. The presence of these working examples favors a finding of adequate enablement especially absent any valid basis to the contrary.

(h) The Quantity of Experimentation Needed to Make or Use the Invention

Appellants do not dispute that some experimentation may be necessary to practice the present invention as defined by the pending claims. Yet "the test [of undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 190 USPQ 214, 217-19, (CCPA 1976)).

MPEP §2164.01 states, complex experimentation is not necessarily undue, if the art typically engages in such experimentation. Appellants respectfully submit that any necessary

experimentation for practicing the full scope of the claimed invention in the instant case would be routine for an ordinarily skilled artisan who is familiar with the well established techniques relating to drug formulation and the preparation of modified release dosage forms given the extensive teaching and direction provided by the subject specification.

3. The Enablement Rejection Is Based on Improper Reasoning

In making the enablement rejection, the Examiner takes the position that the "claims lack the description of the possible genus with the recited functional characteristics". As stated above, the Examiner's rejection is unsubstantiated as well as being erroneous since it is not the purpose of the claims to enable the claimed invention. Rather, enablement of the claims is assessed based on the teachings of the specification and the relevant prior art that was in existence as of the date of invention. For the reasons set forth above, the specification would enable a skilled artisan to practice the genus of modified release tablets having functional properties according to the claims.

4. Summary

The Final Rejection does not articulate a proper prima facie enablement rejection of Claims 155-172 since no legal or scientific basis is provided to substantiate the position that a skilled artisan could not practice the claimed invention absent undue experimentation. In fact, the enablement rejection as set forth in the final rejection reads as if the Examiner intended to make a written description rejection. Even assuming that a proper rejection had been made, such a rejection is unsustainable because the *Wands* factors, when considered as a whole, do not support a finding of undue experimentation. Appellants further contend that the enablement rejection is in error because the Examiner has failed to give appropriate consideration to the specific facts of this application. Accordingly, Appellants respectfully submit that the enablement rejection under 35 U.S.C. §112 of claims 155-172 should be withdrawn.

5. The Enablement of Claims 161 and 162 is Separately Argued

While Appellants respectfully submit that all of the claims are adequately enabled by the teachings of this application, Appellants respectfully submit that the Board separately assess the enablement of Claims 161 and 162. These claims provide for bioequivalent once-daily dosage forms that comprise 150 mg or 300 mg of bupropion. The subject examples particularly exemplify bioequivalent modified release dosage forms containing these amounts of bupropion. These dosage forms falling within the scope of claims 161 and 162 were approved by the FDA and are now in commercial use. At the least, the teachings of the subject application would enable one skilled in the art to produce bioequivalent once-daily dosage forms comprising 150 or 300 mg of bupropion absent undue experimentation.

6. The Enablement of Claim 165 is Separately Argued

Claim 165 further provides for the modified release tablet of claim 155 to posses specific Cmax (maximum blood plasma concentration) and AUC pharmacokinetic parameters on once daily in vivo administration. The subject application provides extensive teaching that would enable a skilled artisan modified-release tablets to produce modified-release tablets that possess such in vivo properties and which are bioequivalent absent the exercise of undue experimentation.

7. The Enablement of Claim 172 is Separately Argued

Claim 172 further limits claim 155 by requiring that the modified-release tablet of claim 155 possess a bupropion containing core which is surrounded by a polymeric control release coating which is in turn surrounded by a polymeric moisture barrier coating. The working examples and the specification herein would clearly enable a skilled artisan to produce a bioequivalent bupropion modified-release tablet having these structural limitations absent the exercise of undue experimentation.

D. The Rejection of Claims 155-172 Under 35 USC §102 is Improper and Should Not Be Sustained

Claims 155-156, 159-162, 165-167 and 169-171 further stand rejected under 35 USC §102(e) as allegedly being anticipated under 35 USC §102(e) by Li et al., US 2003/0161874. The Examiner states as follows:

"Li discloses a sustained release formulation in a form of a tablet or capsule comprising bupropion hydrochloride for once a day administration (abstract; paragraphs 0021, 0024, and 0075). The amount of bupropion is 75-450 mg (paragraph 0028). The formulation is useful for the treatment of depression (paragraph 0022). Li further disclose a Cmax for bupropion at about 8 hours that is 54.2 ng, and AUC 0-inf is 832 ng.hr/ml (table 3). It is noted that Li does not explicitly teach the formulation does not exhibit any food effects. However, it is the examiner's position that this limitation is inherent because Li teaches a formulation that has the same Cmax and AUC values."

The rejection is respectfully traversed because Li does not teach or suggest a once-a-day bupropion tablet formulation that is bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR in Table 3 or anywhere else in their patent application or one which is free of any food effects.

1. Standard for §102 Anticipation Rejection

35 U.S.C §102(e) provides that a person is entitled to a patent unless:

(e) the invention was described in an application for patent, publication under 35 section 122 (b) by another filed in the United States before the invention by the applicants for patent.

Further, in order for a reference (herein earlier-filed and published United States patent application) to anticipate a claimed invention, it must not only disclose all elements of the claimed invention, it must also be enabled. Elan Pharms. Inc. v. Mayo Found. 346 F.3d 1051,1054 (Fed. Cir. 2003). A reference is enabled when its disclosure is sufficient to allow one skilled in the art to make and use the claimed invention . Id. (quoting Bristol Myers Squibb Co.

v. Ben Venue Labs., Inc. 246 F.3d 1368,1374 (Fed. Cir. 2001) Like a patent, a prior art reference is only enabled if its teachings would allow to practice the invention absent undue experimentation. Enzo Biochem. Inc. v. Calgene, Inc. 188 F.3d 1362,1371 (Fed Cir. 1999). Whether "undue experimentation" is required is determined from the perspective of a person of ordinary skill in the art. In re Wands 858 F.2d 731,735 (Fed. Cir. 1988)

2. The §102 Rejection is Unsustainable Because Li Does Not Teach or Suggest a Modified-Release Tablet Formulation That is Bioequivalent to Zyban/Wellbutrin® SR or Wellbutrin® As Claimed Herein

As noted above, a proper anticipatory rejection requires that a single prior art reference teach all the elements of the claimed invention. Herein Li fails to do so because the reference fails to teach or suggest a modified release tablet that is bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR as claimed herein.

This is clear based upon the definition of bioequivalency which is contained in the subject application and applying same to the in vivo pharmacokinetic data contained in the Li reference. As noted supra, in Appellants' traversal of the §112 second paragraph rejection, all the claims pending and under rejection are directed to a modified-release tablet containing bupropion suitable for once a day administration that is "bioequivalent" to the previous commercially available and FDA approved bupropion formulations, i.e., Wellbutrin® and Zyban/Wellbutrin® SR.

The present specification is clear that two different bupropion formulations are bioequivalent only if the 90% confidence interval (CI) of the geometric means of the Cmax, and AUC 0-t or AUC 0-inf parameters (PK parameters) range from 80% to 125%. This is clear for example upon review of Example 8 in the subject application wherein the inventors compared a controlled release bupropion formulation disclosed in the Seth patent, US Patent 6,143,327 to Wellbutrin® and Zyban/Wellbutrin® SR and teach that the Seth formulation is not bioequivalent because the "pharmacokinetic and relative bioavailability data show that the 90% CI for the

formulation as taught in the '327 patent does not fall within the FDA suggested 80%-125% range for a product to be bioequivalent. Accordingly, the data show that the '327 patent formulation is not bioequivalent to the commercially available Zyban/Wellbutrin® SR or Wellbutrin® tablets." (Paragraph [0174] of the instant patent specification)

That "bioequivalent" has this definition is further clearly based on Example 4 of the subject application which compares the in vivo bioavailability of bupropion in a modified-release tablet according to the invention to that of Zyban under fed and fasting conditions. In this example as shown in Tables 17 and 18 the obtained PK data is analyzed in the presence or absence of food and the tablet formulations are determined to be bioequivalent and not to be subject to a food effect "as evidenced by the fact that the 90% CI of the ratio of the geometric means for the AUC 0-inf (and AUC 0-t when appropriate) and Cmax in the fasting vs. fed state fall within the FDA suggested limits of 80-125%." (Last three lines of paragraph [0140])

Therefore, for 2 formulations to be bioequivalent according to the present invention the 90% CI corresponding to the geometric means for Cmax and AUC 0-inf or AUC 0-t must each fall within FDA accepted bioequivalency guidelines which are 80-125%. This test for bioequivalency is not satisfied for the modified release formulations disclosed in the Li patent application. This is the clear from the PK data contained in the Li reference. The only PK data in the patent application wherein the Li formulations are compared to Zyban is contained in Tables 3 and 4. With respect thereto the Examiner has relied on the data in Table 3 as supporting a conclusion that the Li application teaches a tablet formulation bioequivalent to Zyban. In fact, the reverse is true.

Table 3 of the Li application is reproduced below.

TABLE 3

Variable	Example 1 Mean	Zyban Mean	G-Mean Ratio
C_{max} (ng/ml)	54.2	129.0	0.40
$AUC_{0\text{-}inf}$ (ng hr/ml)	832.0	998.0	0.80
T_{lag} (hr)	1.9	0.1	

T_{max} (hr)	8.1	3.6
$T_{1/2}$ (hr)	17.0	20.3

Upon review of the data contained therein it can be seen that the geometric mean ratio of Cmax for their formulation and that for Zyban is 0.40 and the geometric mean of the AUC 0-inf values for the Li formulation and Zyban is 0.80. This data indicates that these formulations are not bioequivalent since these means do not range from 80-125%. In fact for the 90% CI to range from 80-125% as required for bioequivalency, typically the geometric mean ratios for both Cmax and AUC would need to range from about 0.90 to about 1.10. Clearly, based on the reported geometric mean ratios in Table 3 the cited Li patent application bupropion composition is not bioequivalent to Zyban.

Additionally, the foregoing analysis evaluates bioequivalency based on the assumption that the data in Table 3 would even be viewed by a skilled artisan to be probative. However, this is suspect as well since the study reported in Table 3 of the Li patent application is by their own admissions based on only 7 patients. Such a small sample size, even assuming the data was within the 80-125% range for bioequivalency would still likely be deemed unconvincing by a skilled artisan in the field since it is simply too small to draw any reasoned conclusions.

Likewise the remaining PK data which is contained in Table 4 of the patent similarly reveals that Li does not teach and is not in possession of a modified-release tablet that is bioequivalent to Zyban as claimed herein. Table 4 from the Li patent application is also reproduced below.

TABLE 4

Parameter	Example 3	Zyban ®	G-Mean Ratio
C_{max} (ng/ml)	56.9	114.8	0.48
AUC $_{0\text{-inf}}$ (ng hr/ml)	531.7	889.5	0.59
T_{lag} (hr)	1.4	0.1	
T_{max} (hr)	5.1	4.1	
$T_{1/2}$ (hr)	12.6	14.1	

Upon review of the data contained in Table 4 taken from the Li application it can be seen that the geometric means for Cmax and AUC 0-inf when a different formulation according to their invention was compared to Zyban respectively are 0.48 for Cmax and 0.59 for AUC 0-inf. Therefore, again the PK data reveals that the Li tablet formulation is far from bioequivalent to Zyban since the geometric means of these parameters do not range from 80-125%.

The Li reference is only applied under §102(e) and not under 35 USC §103 obviousness. However, even assuming arguendo that it were applied under 35 USC §103 Appellants respectfully submit that the reference would not reasonably suggest or render obvious a once-a-day bupropion modified-release tablet that is bioequivalent to Zyban/Wellbutrin® SR or Wellbutrin® as claimed herein. Particularly, the application provides no expectation of success and provides no suggestion as to how this objective might be accomplished.

For a reference applied under §102 or §103 to render a claimed invention unpatentable it must teach or suggest all elements of the claimed invention and the disclosure must enable one of ordinary skill to practice the claimed invention. The Li reference fails to do so. By contrast, one skilled in the art practicing its teachings would not be placed in possession of a bioequivalent modified-release tablet as clamed herein.

This is apparent based on the PK data contained in the Li patent application reference discussed above. Moreover, the teachings of the Li reference would not enable bioequivalent once-a-day bupropion tablets as claimed herein since the teachings of the reference would not provide one of ordinary skill a means for achieving success (bioequivalent once-daily tablets as claimed herein) absent undue experimentation. Particularly, there are no teachings in the cited Li patent application disclosure which would explain the reason that the bupropion medicaments disclosed in the reference are not bioequivalent. Therefore, the reference would provide a skilled artisan no guidance with respect to the preparation of bioequivalent medicaments as claimed herein. This is to be contrasted with the teachings of the patent

application at issue herein which describes 2 different bioequivalent once-a-day bupropion tablets containing 150 and 300 mg of bupropion and which convincingly demonstrate that they are bioequivalent based on extensive clinical data contained in this application. Also, unlike the present patent application, the Li application does not contain in vitro dissolution data that has been shown to correlate to the desired in vivo outcome (bioequivalency). This further supports a conclusion that the Li patent application would not teach or suggest to one of ordinary skill how to produce a bioequivalent once-a-day bupropion modified-release tablet absent the exercise of undue experimentation. In fact to the best of Appellants' knowledge, the Assignee of the cited application, Andrx Pharmaceuticals, has yet to publicly report or file with the FDA either an ANDA or NDA relating to a bioequivalent bupropion tablet formulation. By contrast 4 other companies have filed such applications with the FDA (after the FDA's approval of the commercial embodiment of the present invention Wellbutrin® XL). This failure is believed to support Appellants' arguments that Andrx was not in possession of a bioequivalent tablet in 1999 when they filed their patent application and based on publicly available information apparently that this situation has not changed even as of the present date.

Claims 156 and 159 Are Separately Argued Based on the Recitation of No Food Effect Therein

Appellants further respectfully note that the Li application does not contain any data that would allow a skilled artisan to conclude that their formulation is free of a food effect. The Examiner in the Final Rejection deems this to be inherent based on the AUC 0-inf and Cmax values reported in Table 3 of the Li patent application. However, this is clearly erroneous. Whether a modified-release dosage form is bioequivalent and free of any food effect can only be assessed by administering the formulation and the comparative formulation to patients in the presence and absence of food and determining whether they are bioequivalent. If these medicaments are bioequivalent and free of any food effect these PK parameters should not significantly vary irrespective of whether the individual is in a fed or fasted state. This data is

not contained in the Li application. By contrast, the only data contained in Tables 3 and 4 would suggest that the Li formulations are not bioequivalent.

The §102 Rejection of Claim 172 is Separately Argued

Claim 172 further provides that the bioequivalent modified-release tablet of claim 155 comprise a bupropion containing core that is surrounded by a polymeric control-release coating which is in turn surrounded by a polymeric moisture barrier coating. The Li patent specification fails to teach or suggest such a bioequivalent dual-coated formulation. Moreover, for the same reasons articulated above the Li application would further fail to enable a bioequivalent dual-coated modified release tablet as set forth in claim 172 absent the exercise of undue experimentation. Particularly, the reference provides no guidance or expectation of success as to how such a bioequivalent medicament might be obtained. Therefore, the §102 rejection of this claim should be reversed.

Appellants' Rebuttal of The §102 Rejection is Further Supported by Andrx' Apparent Failure to Produce a Bioequivalent Once-Daily Bupropion Formulation Even as of the Present Date

In further support of the traversal of the anticipatory rejection based on the Li patent specification Appellants again respectfully note that while this Li application dates back to as early as 1999, that as of the present date Andrx has filed no NDA application with the FDA relating to a once-a-day bupropion tablet formulation or ANDA directed to a bupropion formulation that is bioequivalent to Wellbutrin® XL, the commercial embodiment and FDA approved once-a-day bupropion formulation corresponding to the present invention. This further supports Appellants' arguments (as does Li's own data) that the Andrx inventors were not in possession of a bioequivalent bupropion formulation as claimed in the present patent application.

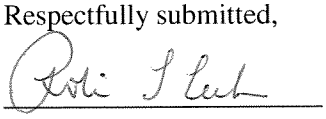
E. CONCLUSION

Based on the foregoing Appellants respectfully submit that claims 155-172 on appeal herein meet the requirements of §112 first and second paragraphs as they are definite and find adequate written description and enabling support based on the teachings of the as-filed application, especially based on the detailed working examples. Therefore, the §112 first and second paragraph rejection of Claims 155-172 should not be sustained.

Also, for the reasons set forth supra, Appellants respectfully submit that the claims on appeal are not anticipated by the Li patent application which fails to teach or suggest or enable a skilled artisan to produce a once-daily modified release tablet that is bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR as claimed in the present invention. Therefore, the §102(e) rejection of claims 155-156, 159-162, 165-167, and 169-171 should also not be sustained.

A favorable decision to that effect is respectfully submitted.

Respectfully submitted,



Robin L. Teskin
Reg. No. 35,030

HUNTON & WILLIAMS LLP
1900 K Street, N.W.
Suite 1200
Washington D.C. 20006-1109
Tel: 202-955-1500
Fax: 202-778-2201
RLT:ast

VIII. CLAIMS APPENDIX

155. A modified-release tablet suitable for use in once-daily administration of bupropion treatment regimen in patients in need of such bupropion administration wherein said modified-release tablet is bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR tablets over a 24 hour period when said modified-release tablet is administered in a once-a-day bupropion treatment regimen to a patient in need of such bupropion administration.

156. The modified release tablet of claim 155 which does not exhibit any food effects.

157. The modified release tablet of claim 155 which includes a moisture barrier.

158. The modified release tablet of claim 155 wherein at least 95% of said bupropion remains undegraded after storage of said modified-release tablet for 18 months t about 25+/- 2 degrees C at 60% RH +/- 5% RH.

159. The modified release tablet of claim 158 which does not exhibit any food effects.

160. The modified-release tablet of claim 155 wherein said bupropion comprise bupropion HCl.

161. The modified release tablet of claim 155 which comprises 150 mg of said bupropion.

162. The modified release tablet of claim 155 which comprises 300 mg of said bupropion.

163. The modified release tablet of claim 157 wherein the amount of said moisture barrier constitutes no more than about 6% of the weight of said modified-release tablet.

164. The modified release tablet of claim 157 wherein the amount of said moisture barrier constitutes no more than about 2.5% of the total weight of said modified-release tablet.

165. The modified-release tablet of claim 155 which when administered in a once-daily bupropion treatment regimen to a patient in need of treatment provides a Cmax for bupropion ranging from about 60ng/ml at between 3 hours and 8 hours (Tmax), an AUC (0-inf) for bupropion ranging from about 800 ng.hr/ml to about 2850 ng.hr/ml

166. The modified release tablet of claim 165 which comprises a 300 mg dose.

167. The modified-release tablet of claim 165 which comprises a 2X150 mg dose administered once-daily.

168. The modified-release tablet of claim 155 which comprises a bupropion containing core which core is surrounded by a control-releasing coat that controls the release of bupropion from the modified-release tablet and a moisture barrier that inhibits the degradation of bupropion contained in said modified-release tablet.

169. A method of treating depression which comprises administering bupropion in a once-daily treatment regimen wherein said bupropion treatment comprises once-daily administration of a modified-release tablet according to any one of claims 155-168.

170. The method of claim 169 wherein said once-daily bupropion treatment regimen comprises administration of said modified-release tablet containing a 300 mg dose.

171. The method of claim 169 wherein said once-daily bupropion treatment regimen comprises daily administration of 2X150 mg of said modified release tablet.

172. The modified-release tablet of claim 155 which comprises:

(i) a bupropion containing core;

(ii) a polymeric control release coating substantially surrounding said core; and

(iii) a polymeric moisture barrier substantially surrounding said polymeric release coating; wherein the polymeric constituents and te amounts thereof contained in said control-release coating and said moisture barrier are selected such that a modified-release tablet is obtained that is bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR tablets over a 24 hour period.

.

IX. EVIDENCE APPENDIX

1. "Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations" March 2003 (obtained from US FDA website on May 31, 2006)

2. "GUIDANCE FOR INDUSTRY Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations" (obtained from US FDA website on May 31, 2006)

X. RELATED PROCEEDINGS APPENDIX

None.